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SULPHARSPHENAMINE.

ITS MANUFACTURE AND ITS CHEMICAL AND CHEMOTHERAPEUTIC PROPERTIES.

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INTRODUCTION.

In this report we propose to describe an arsphenamine derivative which, as far as the laboratory findings and some preliminary clinical observations are concerned, appears to possess certain definite advantages over the arsenicals in use at present in the treatment and control of syphilis. The principal factors which must be considered in the evaluation of such drugs are the following: (1) Therapeutic efficiency (sterilizing power, constancy of therapeutic action of different lots of the drug); (2) a good margin of safety as regards toxic reactions on the part of the patient; and (3) ease of administration. With regard to these requirements, it is safe to state that arsphenamine has been considered the most effective drug from a therapeutic standpoint; but the more or less elaborate method required for its injection and the special precautions (slow rate of injection) necessary to avoid acute toxic reactions have led the clinician to give preference to neoarsphenamine. As a matter of fact, it is evident from the relative ratio of sales of arsphenamine and neoarsphenamine that the latter is probably used in nine cases out of ten which receive arsenical treatment.

The principal reasons for the popularity of neoarsphenamine are simplicity of technique of administration and less stringent safety requirements for its intravenous injection. But neoarsphenamine, from the chemical and pharmacological point of view, is a drug of uncertain chemical composition, and its solutions are very unstable. Ehrlich (1913) and Voegtlin and Smith (1920) have shown that solutions of neoarsphenamine undergo gradual oxidation, accompanied by an increase in toxicity, amounting to several hundred per cent, and Roth (1920) has discovered that moderate shaking of neoarsphenamine solutions with air at room temperature for a few minutes will accelerate this decomposition enormously. These observations were recently confirmed by Schamberg, Kolmer, and Raiziss (1922). Voegtlin and Smith (1921) and Voegtlin and Miller

(1922) have furthermore found that the parasitocidal power of different batches of neoarsphenamine show variations amounting to 300 per cent, observations which were confirmed and extended by Dale and White (1922) in England.

These findings have led to the adoption of the trypanocidal test in order to insure as far as possible constancy of the drug in the form in which it is put on the market. We believe, however, that these additional safeguards will not completely assure constancy of therapeutic potency under ordinary conditions. First of all, Roth (1921) has shown that about 25–30 per cent of commercial neoarsphenamine deteriorates in the ampule in the course of time; and, furthermore, no assurance exists that the physician using the drug will not manipulate its solution in such a way as to avoid partial decomposition. A further important objection to neoarsphenamine is the fact that it has to be injected intravenously; and as was pointed out in a recent address by Voegtlin (1922), intravenous medication should only be resorted to as a last resort, when, for one reason or another, other routes are contraindicated.

We believe that the new arsphenamine derivative, to be described under the name of sulpharsphenamine, will meet these objections.

MANUFACTURE.

Sulpharsphenamine is prepared from arsphenamine, formaldehyde, and sodium bisulphite, according to the following directions:

The preparation is carried out in two principal stages: (1) Formaldehyde is allowed to react upon arsphenamine (the hydrochloride) with the formation of a condensation product having the formaldehyde attached to both amino groups (formaldehydimide derivative), and (2) the formation of a sulphurous acid ester salt by the addition of sodium bisulphite to the formaldehydimide compound. The theoretical chemical questions involved in these reactions are discussed in a paper which is in press at the time this article is being written.

Preparation of Lot 1420: To 50 gm. of arsphenamine (1 mol.) is added 75 c. c. 95 per cent alcohol, the mixture being stirred thoroughly. The drug is then dissolved at about 20° C. by the addition of 675 c. c. of water, using an efficient mechanical stirring device. After complete solution is obtained, 18.15 c. c. of 33.8 per cent formaldehyde (2 mol.) is added rapidly under vigorous stirring, and about a minute later 65 c. c. of 32.64 per cent of sodium bisulphite (2 mol.) at once. The light yellow precipitate, which forms immediately with the liberation of SO_2 , gradually redissolves as stirring is continued. After about 10 minutes another 65 c. c. of the same bisulphite solution (2 mol.) is added, and the stirring is continued. A very slight amount of undissolved material is separated, and the dark orange solution is poured in a fine stream under vigorous stirring into 4,040 c. c. of 95 per cent alcohol. The light yellow precipitate is filtered off, washed with 95 per cent alcohol, followed by absolute alcohol, and the product is dried in vacuum over caustic soda. Yield, 64 gm.

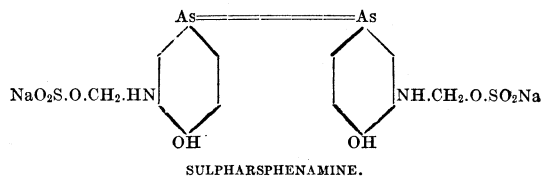
Several conditions must be observed for the successful preparation of this drug: (1) The solution of arsphenamine must be complete before the formaldehyde is added (alcohol facilitates the rapidity of solution and also has a tendency to prevent the formation of a jelly after the addition of formaldehyde); (2) sufficient time should elapse to allow the formaldehyde to react with arsphenamine—usually one minute—but not enough time to cause the formation of a viscous mass which will not readily dissolve upon the addition of bisulphite; (3) the bisulphite should be added in two portions, each portion being added rapidly about seven minutes apart; (4) the formaldehyde and bisulphite solutions should be analyzed for their strength; (5) the bisulphite must be prepared freshly from Na_2CO_3 and SO_2 ; (6) 2 mol. of formaldehyde and 4 mol. of bisulphite per 1 mol. of arsphenamine are usually satisfactory, though 3 mol. of formaldehyde and 6 mol. of bisulphite seem to be more favorable proportions.

For the calculation of molecular proportions of arsphenamine, formaldehyde, and bisulphite the actual arsenic content of arsphenamine was taken as a basis, and the strength of formaldehyde and bisulphite was determined quantitatively.

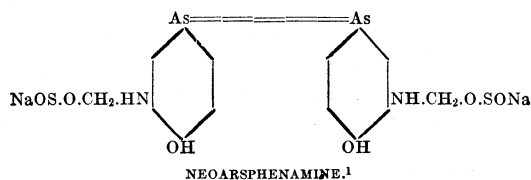
The manufacture was also tried out on a larger scale, using a batch of 1 kilogram of arsphenamine. The reactions proceeded with even greater ease than when smaller quantities were used, and the yield was very satisfactory. On account of the relative cheapness of the reagents required and of the slightness of the chance of losing a batch, the product ought not to be more expensive than arsphenamine, a point which is of importance when consideration is given to the enormous quantities of the arsenicals used in the control of syphilis.

CHEMICAL AND PHYSICAL PROPERTIES.

As will be shown in another publication, the arsenic is present as a compound of the following constitution:



Sulpharsphenamine has, therefore, a side chain differing from that of neoarsphenamine by the presence of one additional atom of oxygen.



¹ Commercial neoarsphenamine may be a mono- or di-substitution product or a mixture of the two.

The free acid of sulpharsphenamine was isolated by treatment with glacial acetic acid and on analysis yielded a ratio As : N : S of 1 : 1 : 1, which is to be expected of a di-substitution product.

Sulpharsphenamine is a light yellowish powder, the appearance of which on exposure for days to moderately dry air does not change. It dissolves with the greatest ease in cold water, forming a yellow to orange solution according to concentration. Ten per cent and stronger solutions, after several days standing, form a yellow jelly, indicating the colloidal nature of the drug. No color change takes place, however, on exposing aqueous solutions to air at room temperature even for weeks (contrast to neoarsphenamine, which gradually assumes a dark greenish brown appearance). The hydrogen ion concentration of a 1 per cent solution of 20 different batches, determined by means of bromphenol-blue and methyl-red varied between 3.2 and 4.6, the reaction, therefore, being decidedly on the acid side. Freezing point determinations gave average values of 2.6 and 4.6 atmospheres for 5 and 10 per cent solutions, respectively. Physiological saline (0.85 per cent NaCl) has an osmotic pressure of 6.14 atmospheres. Ten per cent sulpharsphenamine is therefore considerably hypotonic with respect to blood. The drug yields the same qualitative tests as neoarsphenamine (Myers and DuMez).

A simple test to differentiate between sulpharsphenamine and neoarsphenamine consists in treating the solutions with a few drops of an indigocarmin solution, which is decolorized by neoarsphenamine but not by sulpharsphenamine. When the solution of the latter is reduced with a little zinc dust and acetic acid, the filtrate will then reduce the dye. This test, if positive, indicates a group $\equiv\text{C.O.SONa}$. Reduction of sulpharsphenamine with zinc changes the side chain $-\text{NH.CH}_2.\text{O.SO}_2\text{Na}$ to $-\text{NH.CH}_2.\text{O.SONa}$, that of neoarsphenamine.

TABLE I.—Summary of preparation of various lots of sulpharsphenamine and their composition.

Lot No.	Arsphenamine used. (Grams.)	Solvent. (Parts.)	HCHO. (Mol.)	NaHSO. (Mol.)	Yield. (Grams.)	Nitrogen. (Percent.)	Arsenic. (Per cent.)	Sulphur. (Per cent.)	Atomic ratio. (As:S.)
1364...	5	15 H ₂ O.....	2	4	5.9	3.93	21.67	12.13	1:1.31
1366...	5	do.....	2	4	5.5	4.12	22.45	12.14	1:1.26
1369...	50	do.....	2	4	61.0	4.00	21.80	11.68	1:1.25
1390...	10	do.....	2	4	5.4	3.85	23.81	11.47	1:1.12
1391...	50	do.....	2	4	63.0	4.22	22.24	11.04	1:1.16
1393...	5	{1.5 alcohol.....}	2	4	6.0	4.09	23.47	10.85	1:1.08
1395...	5	{13.5 H ₂ O.....}	2	4	4.0	4.04	23.74	10.22	1:1.01
1398...	5	do.....	2	4	5.0	3.90	23.16	10.82	1:1.09
1399...	5	{1.5 alcohol.....}	2	4	6.0	4.11	23.60	10.95	1:1.08
1400...	30	do.....	2	2	36.0	4.25	22.32	8.72	1:0.91
1413...	10	do.....	2	4	11.9	3.92	21.31	11.21	1:1.23
1414...	7	do.....	2	4	7.2	4.13	23.05	10.89	1:1.10
1415...	4.8	do.....	2	4	3.8	4.00	22.06	10.85	1:1.15
1420...	50	do.....	2	4	64.0	3.95	21.68	10.48	1:1.13
1426...	10	do.....	3	4	14.5	3.53	19.40	11.99	1:1.44
1428...	10	do.....	3	6	11.4	3.89	21.68	10.48	1:1.22
1451...	10	do.....	3	6	13.0	3.63	20.77	12.88	1:1.45
1593...	1,000	do.....	2.25	4	1120.0		23.60	9.86	1:0.93

The average arsenic content of sulpharsphenamine is 22 per cent, of arsphenamine 30 per cent, and of nearsphenamine 18 to 20 per cent. The impurities which lower the arsenic content of sulpharsphenamine below the theoretical (25.06 per cent As for disodium salt) are principally inorganic salts, as in the case of nearsphenamine. Table I gives a summary of the preparation of the various lots made and their composition. It may suffice here to call attention to the fair constancy of the product, and this in spite of the fact that arsphenamine obtained from different manufacturers was used—in some cases, even, batches which did not meet the official requirements of the toxicity test. The large batch (Lot 1593) was made from miscellaneous ampules of arsphenamine which had accumulated during the past three years.²

METHOD OF ADMINISTRATION.

Sulpharsphenamine is as well tolerated when injected intravenously as is nearsphenamine. Intramuscular injections of concentrated solutions cause some local reaction, which is, however, much less severe than that following similar injections of arsphenamine or nearsphenamine. The principal advantage of sulpharsphenamine is that it can be injected subcutaneously with impunity, provided that for full therapeutic doses the concentration is kept high (20 to 30 per cent). Lieutenant Commander Powell, United States Navy, who very kindly performed some preliminary clinical tests, found that a 20 per cent solution (0.4 to 0.6 gm.) injected into the subscapular region is well tolerated, whereas the same doses given in 5 or 10 per cent solution produced some local edema, which, however, disappeared within a few days, leaving no noticeable change. Dilute solutions produce a slight burning sensation at the site of injection, this lasting only a very short time.

TOXICITY.

The toxicity was established in albino rats, using the official intravenous technique, and also by subcutaneous injection in rats. The intravenous injection is well tolerated when doses up to about two-thirds of the M. L. D. are used. Higher doses very often produce diarrhea with or without the appearance of blood in the feces, muscular weakness, and, at times, hematuria. After lethal doses slight tremors of the whole body are sometimes in evidence, lasting until death.

² Sulfarsenol, a product manufactured by Laboratoire de Biochimie médicale (R. Pluchon), is a product which is similar to the product described by us, but its method of preparation has been kept a trade secret.

A German patent (D R P 249726) refers to a reddish brown product made by prolonged heating on the water bath of arsphenamine base, formaldehyde, and sodium bisulphite. We have repeated the preparation of this product, following minutely the directions given in the patent, and have obtained a reddish product differing in many essential chemical, physical, and biologic properties from sulpharsphenamine. The method described in this paper is therefore original, as will be seen from the above data.

There is always a considerable gain in body weight during the week following the injection, and this is quite pronounced even with slightly sublethal doses, which indicates that the drug does not in any way interfere with the growth of the animal.

TABLE II.—*Toxicity and trypanocidal action of intravenous and subcutaneous sulpharsphenamine injections in rats.*

Lot No.	Minimum lethal dose. (Mg. per kilo.)		Minimum effective dose. (Mg. per kilo.)		Lot No.	Minimum lethal dose. (Mg. per kilo.)		Minimum effective dose. (Mg. per kilo.)	
	Intra-venous.	Subcuta-neous.	Intra-venous.	Subcuta-neous.		Intra-venous.	Subcuta-neous.	Intra-venous.	Subcuta-neous.
1364.....	380	400	26	26	1400.....	360	570	16.8	25.2
1366.....	480	400	16.7	25	1413.....	400	620	26.4	26.4
1389.....	400	470	25.8	25.8	1414.....	360	520	24.0	24.0
1390.....	440	700	31.5	23.4	1415.....	400	570	17.0	34.0
1391.....	400	640	16.8	25.2	1420.....	440	570	26.0	17.3
1393.....	360	470	15.9	23.8	1426.....	420	570	28.9	28.9
1395.....	320	500	23.7	15.6	1428.....	380	470	26.0	26.0
1398.....	400	560	24.3	24.3	1451.....	440	570	27.0	27.0
1399.....	360	420	15.9	31.8	1593.....	400		23.8	

The necropsy findings are not at all constant and consist in congestion of the lungs, increase in pleural fluid, hemorrhages in the intestinal wall, and congestion or paleness of the kidneys and liver.

Table II gives a summary of the toxicity work with rats. It will be seen that, using the intravenous injection, the most toxic preparation is Lot 1395 (M. L. D. 320 mg. per kilo); the least toxic Lot 1366 (M. L. D. 480 mg. per kilo). The official regulations governing the sale of arsphenamine require that arsphenamine shall have a maximum tolerated dose not below 120 mg. per kilo, and neoarsphenamine must pass at least at 200 mg. per kilo. It is evident, then, that these preparations of sulpharsphenamine are far less toxic than preparations of arsphenamine or neoarsphenamine which just fulfill the official requirements. This difference between the three drugs is still more pronounced when the toxicity of subcutaneous injections of sulpharsphenamine is considered, a fact which justifies the conclusion that sulpharsphenamine is a drug of extremely low toxicity as compared with that of arsphenamine and neoarsphenamine. Reference is here made to an examination of the toxicity of commercial samples of arsphenamine and neoarsphenamine of recent manufacture which will emphasize this point (Carl Voegtlin and D. W. Miller, 1922).

Chart 1 illustrates the mortality rate of rats dying within the first week following intravenous injection and is presented principally for the purpose of comparing the mortality rate of arsphenamine and sulpharsphenamine under identical conditions. It will be noted that both drugs cause death acutely in the large majority of animals, 87 per cent within 24 hours with arsphenamine and 56 per cent with sulpharsphenamine. On the whole, the length of life after

injection of sulpharsphenamine is slightly longer than that following the injection of arsphenamine. This point is of importance for the official toxicity control of this drug, and we suggest here that the period of observation for the determination of toxicity be four days.

The mortality rate after *subcutaneous* injection in rats is practically

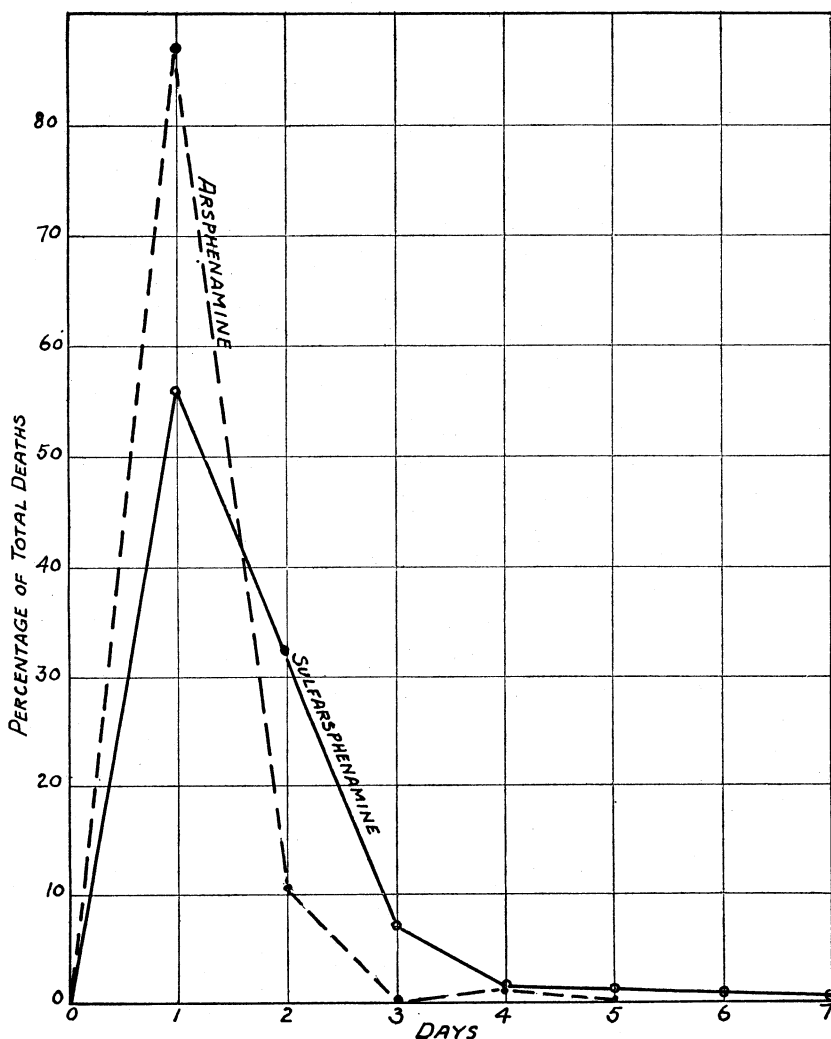


CHART 1.—Comparison of mortality among rats, following injections of arsphenamine and sulpharsphenamine.

the same as the one for intravenous injection, and for this reason has been omitted in Chart 1.

The toxicity of an average preparation (Lot 1391) was also established by intravenous injection into rabbits, and a minimum lethal dose of 320 mg. per kilo was found. In rats the M. L. D. of the

same preparation was 400 mg. per kilo. This finding conforms with other experience regarding the relative toxicity of arsphenamine derivatives in these two species, the rabbit being somewhat more susceptible than albino rats.

The work so far discussed always dealt with freshly prepared solutions. It was of interest to study the stability of such solutions on standing in contact with air in an open vessel at ordinary room temperature, and also to determine whether the toxicity of solutions of the drug increased as a result of vigorous shaking.

Solutions were made from lots 1389, 1390, and 1391, and were allowed to stand in open graduated cylinders for 24 hours, at the end of which time the solutions were tested for toxicity, with the result that the toxicity figures obtained did not in the slightest degree vary from those for freshly prepared solutions. Solutions of the same three preparations were also vigorously shaken in glass cylinders with air for 10 minutes without producing any change in toxicity. The conclusion is therefore justified that aqueous solutions of sulpharsphenamine are very stable indeed, which is in striking contrast to solutions of the disodium salt of arsphenamine and particularly of neoarsphenamine. These observations would therefore constitute an absolute safeguard against decomposition of sulpharsphenamine in its clinical use, a point which is of very considerable importance with regard to the elimination of toxic reactions in the patient due to this cause.

A further advantage of sulpharsphenamine is that in its preparation the use of arsphenamine which just fails to pass the official toxicity test yields sulpharsphenamine of good quality, passing the toxicity test as high as other material prepared from much less toxic arsphenamine.

TRYPANOCIDAL POWER.

For the determination of the trypanocidal power of our preparations the technique worked out during the last few years in this laboratory, and described in detail by Voegtlin and Miller (1922), was used with this modification, namely, that a four-day period of observation was chosen in preference to the 24-hour period.

TABLE III.—*Minimum effective dose at different time intervals following treatment.*

[Doses expressed as c. c. 1/100 arsenic equivalent solution per kilo body weight. Intravenous=Iv.; subcutaneous=Sc.]

Lot No.	24 hours.		48 hours.		72 hours.		96 hours.		120 hours.		144 hours.	
	Iv.	Sc.	Iv.	Sc.	Iv.	Sc.	Iv.	Sc.	Iv.	Sc.	Iv.	Sc.
1364.....	15.0	15.0	7.5	7.5	7.5	7.5	5.0	7.5	5.0	7.5	5.0	7.5
1366.....	10.0	15.0	10.0	10.0	10.0	7.5	7.5	7.5	7.5	7.5	7.5	7.5
1389.....	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
1390.....	10.0	10.0	10.0	10.0	10.0	7.5	10.0	7.5	10.0	7.5	10.0	7.5
1391.....	10.0	10.0	7.5	10.0	7.5	10.0	7.5	10.0	7.5	7.5	5.0	7.5
1393.....	10.0	10.0	7.5	7.5	7.5	7.5	5.0	7.5	5.0	7.5	5.0	7.5
1395.....	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	5.0
1398.....	10.0	10.0	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
1399.....	7.5	10.0	7.5	10.0	7.5	10.0	5.0	7.5	5.0	7.5	5.0	7.5
1400.....	7.5	10.0	7.5	10.0	7.5	10.0	5.0	7.5	5.0	7.5	5.0	7.5
1413.....	10.0	10.0	10.0	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
1414.....	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
1415.....	7.5	10.0	7.5	10.0	7.5	10.0	7.5	10.0	5.0	10.0	5.0	10.0
1420.....	10.0	7.5	7.5	7.5	7.5	7.5	7.5	5.0	7.5	5.0	7.5	5.0
1426.....	10.0	10.0	10.0	10.0	10.0	10.0	7.5	7.5	7.5	7.5	7.5	7.5
1428.....	10.0	10.0	7.5	10.0	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
1451.....	10.0	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
1593.....	10.0				7.5		7.5		7.5		7.5	

We have had several occasions to point out that this trypanocidal test yields very satisfactory evidence with regard to the parasitocidal action of arsenicals and permits a biological assay of the relative value of different arsenicals with regard to their spirocheticidal action. The results obtained with this test in rats infected with *Trypanosoma equiperdum* are summarized in Table II and need very little comment. Attention is called to the considerable constancy of the trypanocidal power of the different sulpharsphenamine preparations, no matter whether the drug is administered by vein or subcutaneously. Such extreme variations as are found between different neoarsphenamines are totally absent; i. e., the method of preparation as described in this paper yields products of fairly constant parasitocidal value, and this in spite of the fact that arsphenamine of varying toxicity and manufacture was used. The average minimum effective dose is 7.5 c. c., which is identical with that of the average commercial neoarsphenamine on the market at the present time. From Table III it is evident that the maximum parasitocidal effect is not always reached in 24 hours, but often only after 3 or 4 days. This is in striking contrast with our experience with arsphenamine and neoarsphenamine, drugs which produce their maximum effect in 24 hours. Sulpharsphenamine must therefore be considered as acting more slowly upon the parasites than the other arsphenamines. Should this hold true for the spirocheticidal action of sulpharsphenamine, and there is no obvious reason to doubt it, this property might constitute another advantage over the well-known arsphenamines, on the ground that a slow action of the drug upon the parasites might tend to prevent the occurrence of reactions due to the liberation of spirochetal material following the

rapid breakdown of parasites. On theoretical grounds, a remedy with slow action on the syphilitic process would have to be given preference.

As a further illustration of the rate of parasitocidal action of sulpharsphenamine, attention is called to Chart 2, which represents the so-called action curves of one and one-half the minimum effective dose of arsphenamine and sulpharsphenamine. Three rats were used for each group experiment, arsphenamine being injected intravenously; sulpharsphenamine either intravenously or subcutaneously. The initial trypanosome count was taken immediately before treatment, and the count was followed thereafter at intervals. The blood of all animals was free from parasites 24 hours after treatment; yet the speed of the disappearance of the parasites differed very considerably, arsphenamine acting most rapidly, sulpharsphenamine given subcutaneously coming next, and then, slowest of all, sulpharsphenamine given intravenously. In the latter experiments, over six hours elapsed before the first parasites died. We have no explanation of this difference in the behavior of these two drugs and can only suggest that it may be due to differences in the rate of their breakdown in the body to the corresponding single ring trivalent arsenious oxide compounds, which, as we have shown previously (Voegtlin and Smith, 1920), represent the active modification of all arsenicals.

The figures given for the minimum effective dose are a measure of the killing power of the drug for a definite number of trypanosomes. It is of interest, of course, to know also the sterilizing effect of a given dose, i. e., the dose which will cure the animal permanently of the infection. In Table IV data are presented which give information as to the percentage of animals, treated with the different arsenicals, which relapsed after having been treated with 1, 1½, 2, or 3 minimum effective doses of arsphenamine, neoarsphenamine, and sulpharsphenamine. The period of observation necessary to determine whether or not an animal was permanently cured was 30 days. It will be seen from Table IV that sulpharsphenamine given subcutaneously produces a greater percentage of cures than the other arsenicals.

TABLE IV.—*Comparison of relapses after treatment with arsphenamine, neoarsphenamine, and sulpharsphenamine in rats infected with Tr. equiperdum.*

Preparation and method of administration.	Percentage of relapses.			
	M. E. D.	1½ M. E. D.	2 M. E. D.	3 M. E. D.
Arsphenamine, intravenously	91.6	72.2	10.0	43.7
Neoarsphenamine, intravenously	50.0	33.3	0.0	
Sulpharsphenamine, intravenously	53.6	20.5	4.5	
Sulpharsphenamine, subcutaneously	34.2	8.8	0.0	

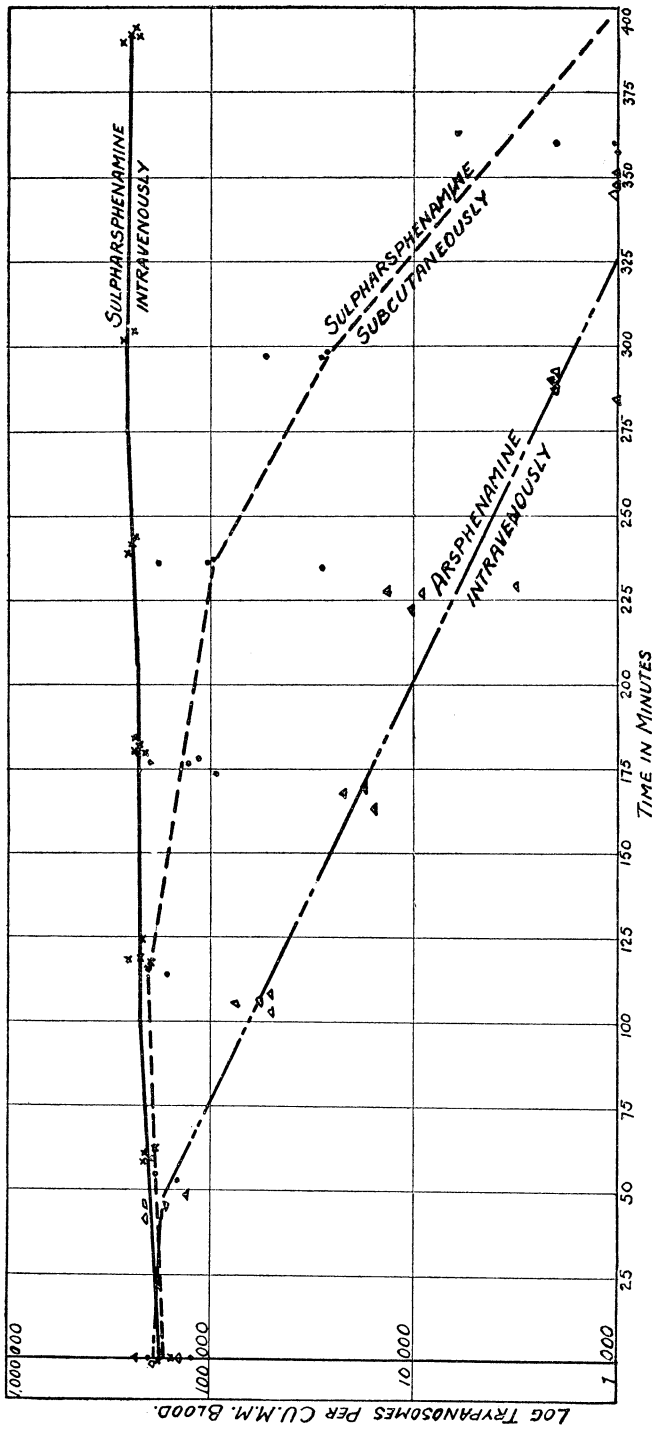


CHART 2.—Comparison of rates of parasitocidal action of arsenphenamine and sulpharsphenamine.—Action curves of one and one-half the minimum effective dose of arsenphenamine and sulpharsphenamine.

SPIROCHETICIDAL POWER.

In order to furnish additional evidence of the probable value of sulpharsphenamine in the treatment of syphilis and other related spirochete infections, it was deemed necessary to determine the relative value of the new drug and arsphenamine and neoarsphenamine on rabbits infected with the Nichols's strain of *Spirocheta pallida*. A series of rabbits was inoculated with this strain, and, after pronounced chancres had been produced, some of the rabbits were treated by single intravenous injections of graded doses of a German neoarsphenamine (M. E. D. 5 c. c.). Another set of syphilitic rabbits received subcutaneous injections of a 10 per cent sulpharsphenamine solution (M. E. D. 7.5 c. c.), also in graded doses. Table V shows that in all rabbits the spirochetes had completely disappeared from the lesions 24 hours after treatment. The doses used were selected on the basis of the work of Ehrlich and Hata (1910), dealing with the spirocheticidal effect of arsphenamine. According to these authors, single doses of arsphenamine of 15 mg. per kilo cause the disappearance of parasites from the lesions; with a dose of 5-10 mg. per kilo, the parasites are still in evidence for two days; smaller doses are ineffective. When compared with our figures for sulpharsphenamine, it is obvious that a subcutaneous injection of 15 mg. per kilo of this drug is at least as effective as the same dose of arsphenamine, yet sulpharsphenamine Lot No. 1451 contains 20.77 per cent arsenic, whereas arsphenamine contains on the average 30 per cent. On the arsenic basis, sulpharsphenamine has, therefore, a higher spirocheticidal value than arsphenamine. Commander Powell, U. S. N. Medical Corps, informed us that one case of primary syphilis in a sailor treated with 0.4 gram of sulpharsphenamine showed complete disappearance of spirochetes from the chancre after 24 hours, an observation which is in harmony with what has just been stated.

TABLE V.—*Spirocheticidal action of nearsphenamine and sulpharsphenamine (1451) on rabbits.*

No. and weight of animal.	Subcutaneous inoculation of Nichols's Treponema pallidum, July 17, 1922, on—	Microscopic and macroscopic examination of lesions before treatment, Sept. 25, 1922.	Intravenous. Dose of nearsphenamine, G. 1401. (10 per cent solvent used.)		24-hour microscopic examination.	Further examination of lesions.
			Mg. per kilo.	c. c. 1/100 As equivalent.		
8. Wgt., 227.	Left testicle.	Wgt., 1.72. Chancre in both glands. Right: Marked induration, with black crust $\frac{1}{4}$ cm. in diameter; spirochetes fairly numerous. Left: Marked induration; bloody exudate showing a few organisms. Puncture fluid: Spirochetes very numerous. Wassermann, + + + +.	15	4.06	1 doubtful spirochete found in examination of several specimens from left gland. Negative from right gland.	Sept. 28: Micros. exam. neg. Right side indurated. Swelling gone down. Left gland indurated; small amount of bloody fluid still oozing out. Oct. 2: No induration. Black crust still present. Micros. exam. neg.
4. Wgt., 2166	Left testicle.	Wgt., 2.26. Large black crust $1\frac{1}{4}$ cm. in diameter, with much induration of left gland. Wassermann, + + + +. Fluid taken from periphery of crust shows more than 100 spirochetes per field.	27	7.3	Negative from left gland.	Sept. 28: Considerable shrinkage of induration. Micros. exam. neg. Oct. 2: Induration almost completely gone. Small, reddish scar $\frac{1}{4}$ mm. diameter. Oct. 10: Lesion practically healed; small scar.
3. Wgt., 1.64.	Right testicle	Wgt., 1.65. Both testicles hard. Left shows no superficial lesion. 3-4 spirochetes per field. Right shows small superficial crust. Countless spirochetes per field. Wassermann, + + + +.	36	9.7	Negative from right gland.	Sept. 28: Induration much less marked in both glands. Micros. exam. neg. Oct. 2: Slight induration in both glands. Small crust 3 mm. diam. on left. Crust gone from right; practically healed. Oct. 10: Both glands healed.
7. Wgt., 217.	Left testicle.	Wgt., 2.2. Right gland normal. Left shows large chancre, black, hard crust $1\frac{1}{4}$ cm. in diameter, with much induration. Wassermann, + + + +. Spirochetes countless per field.	15	4.16	Negative in 2 preparations from left gland.	Sept. 28: Induration less marked. Micros. exam. neg. Oct. 2: Slight induration still present. Black crust unchanged in appearance. Oct. 10: Unchanged. Micros. exam. neg.

TABLE V.—*Spirocheticidal action of nearsphenamine and sulpharsphenamine (1451) on rabbits—Continued.*

No. and weight of animal.	Subcutaneous inoculation of Nichols's Treponema pallidum, July 17, 1922, on—	Microscopic and macroscopic examination of lesions before treatment, Sept. 25, 1922.	Subcutaneous. Dose of sulpharsphenamine, P. 1451. (10 per cent solvent used.)		24-hour microscopic examination.	Further examination of lesions.
			Mg. per kilo.	c. c. 1/100 As equivalent.		
2. Wgt., 2.0..	Left testicle.	Wgt., 2.07. Large chancre 1 cm. in diameter in left testicle, with considerable induration of gland. Wassermann, + + + +. Spirochetes countless per field.	27	7.5	Negative from left gland.	Sept. 28: Induration less marked. Micros. exam. neg. Oct. 2: No induration. Black crust unchanged in appearance. Oct. 10: Scab 4 mm. in diam.
6. Wgt., 2.29.	Left testicle.	Wgt., 2.67. Large chancre in left testicle, with hard black crust 1 cm. in diameter. Marked induration of gland. Wassermann, + + + +. Spirochetes countless per field.	36	10.0	Negative from left gland.	Sept. 28: Less induration. Micros. exam. neg. Oct. 2: Practically no induration. Black scab 1 cm. in diam. Oct. 10: Black scab fallen off; small new scab formed.
5. Wgt., 2.18.	Left testicle.	Wgt., 2.28. Left testicle shows an indurated area 1 cm. in diameter covered with black protruding crust. Wassermann, + + + +. Puncture juice shows one definite spirochete.	50	13.8	Negative from left gland.	Sept. 28: Induration slightly less. Oct. 2: No induration. Crust still present. Oct. 10: Small scab 2 mm. in diam.

A further interesting deduction to be made from these data is that whereas 7.5 c. c. 1/100 arsenic equivalent solution per kilo body weight of sulpharsphenamine is required to clear the blood of rats from trypanosomes, 4.16 c. c., or probably less, is sufficient to clear the lesions of syphilitic rabbits, i. e., less arsenic is necessary in the rabbit than in the rat. This may be due to the greater number of parasites present in the body of the rat as compared with the number of parasites in the rabbit, and would confirm again some of our older work on the relation between size of dose and number of parasites killed.

Furthermore, a comparison of the toxicity and parasitidal value of the various lots of sulpharsphenamine shows that the chemotherapeutic index, or the margin of safety, of this drug is at least as good as that of the most potent drug so far known, namely arsphenamine.

SUMMARY.

The data presented show that sulpharsphenamine is an arsphenamine derivative very closely related in chemical structure to neoarsphenamine. This slight change in chemical constitution, however, imparts to the drug certain definite advantages over neoarsphenamine, as (1) ease of manufacture, (2) great stability of drug in the dry form and in watery solutions, (3) constancy of toxic and parasitidal action of different lots, and (4) suitability for hypodermic administration. Every one of these advantages is of far-reaching importance, when consideration is given to the fact that enormous numbers of doses of arsphenamine are used in the control of syphilis.

As far as the experimental evidence is concerned, the above-mentioned advantages of sulpharsphenamine are firmly established. However, we strongly emphasize that before this drug can be introduced for general use, it will be necessary to give it an exhaustive trial as to its curative power in human syphilis. There is no way to predict the outcome of this trial. The clinical studies especially will have to consider whether or not sulpharsphenamine has, for normal and syphilitic tissue, the same penetrating power as, or better than, arsphenamine and neoarsphenamine. After all, the main difficulty with the arsenicals in present use appears to consist in their failure to reach the last spirochetes which may be buried in lesions that are difficultly accessible. It is obvious that incomplete sterilization of the patient due to this cause will prevent a cure and will cause, sooner or later, clinical relapses. In this respect syphilis differs markedly from diseases due to organisms which are closely related to *Treponema pallidum*. Yaws and relapsing fever may be cured with a single injection, or a few injections, of arsphenamine. This is of particular significance in view of the fact that the parasite responsible for yaws

is morphologically and in other ways so similar to *Treponema pallidum* that certain investigators consider the former as merely a different strain of the latter organism. Hence, the most reasonable explanation of the difference in the curative power of arsphenamine in syphilis, on the one hand, and yaws and relapsing fever on the other, is probably to be found in the specific pathology of syphilis, which favors the hiding of parasites in recesses inaccessible to arsphenamine. We suggest that sulpharsphenamine be given a clinical trial, particularly in patients with difficulty accessible veins (adipose patients, infants), and cases which exhibit an unusual idiosyncrasy to intravenous treatment. In view of the fact that the parasitocidal action of sulpharsphenamine is slower than that of the arsphenamine, the former drug might be of use in cases with indications of an extensive syphilitic involvement of the cardiovascular system, in which a slow action of the remedy is desirable. Under these conditions a subcutaneous injection of sulpharsphenamine should be of value on account of the gradual absorption of the drug.

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NUTRITION AND EDUCATION.

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Two insistent questions arise in the minds of thoughtful parents everywhere: Shall I send my child to school as soon as the law says he is old enough to go, or would it be better for his health if I kept him out till he is older? If he seems brighter than the average child, will it be detrimental to his health to permit him to be "accelerated"—to make as rapid progress through the school grades as his teachers desire?

The answers to these questions, from both physicians and educators, have been usually merely an expression of opinion colored by the viewpoint of the person consulted. In view of the contradictory character of the data on which a reply to such questions might be in some measure based, and in order to study the subject in what might be called a fairly typical American community, the present investi-